Cancer Preventive Drug Development: Challenges and Opportunities

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Clinical Agent Development – What are the major issues?

- Targets/agent selection – correctly match target/agent to right process/person (Precision Medicine)
- Risk-benefit balance
- Cohort selection
- Recognizing efficacy during early clinical development
- Clinical trial designs
What are the major challenges?

Target identification

- Understanding early carcinogenesis
  - Difficult (but necessary) to study premalignancy longitudinally (small lesions, not easily accessible, repeated samplings)

- Understanding the carcinogenic process in a given individual (here and now) is challenging

-Campbell JD et al., CaPR 2016
What are the major challenges?

Target identification

- Biology
  - Heterogeneity – between and within individuals
    - Spatial and temporal diversity in cancer evolution
    - Different processes operational during different phases of carcinogenesis
      - e.g., tobacco mutational spectrum early followed by APOBEC-associated mutations later in smokers developing NSCLC

- [De Bruin et al., Science 2014]
Optimizing Risk/Benefit – Topical Approaches

Breast Cancer

- Topical 4-hydroxytamoxifen (4-OHT)- small phase II topical 4-OHT vs. oral tamoxifen (T) in DCIS for 6-10 weeks pre surgery
  - ↓ Ki-67 post Rx: 3.4% 4-OHT vs. 5.1% T (P<0.03 in both, between-group P=0.99)
  - Endocrine/coagulation biomarker effects reduced by 4-OHT; no difference in hot flashes

- Topical telapristone trial – oral vs. topical Rx, presurgical trial
  - Anti-progestin, based on robust preclinical data, biodistribution within the breast
    - DCP Consortium trial, PI: Seema Khan, NWU
Minimizing Toxicity – Intermittent Dosing Regimens

- Mouse MNU-carcinogenesis prevention study – similar efficacy with daily, 2-days on/2-days off, weekly regimens
- Multiple trials of intermittent dosing, using different drugs, ongoing

- Erlotinib
  - B1 - daily 6 mg/kg
  - B2 - 2d on, 2 d off – 6mg/kg
  - B3 - once weekly, 42 mg/kg
  - No Rx

-Lubet RA et al., Cancer Prev Res 2013;6:448-454
Identification of High Risk Cohorts
Example: Oral Cancer

- Dysplastic oral leukoplakia
  - 11-36% progression to cancer over 7+ yrs
  - 26% with 3p14 and/or 9p21 LOH develop cancer in 5 yrs
  - 47% with 3p14 and/or 9p21 LOH and one other LOH site develop cancer in 5 yrs
    - Rosin et al., CCR 2000;6:357-62

- EPOC trial – cancer endpoint
  - William et al., JAMA Oncol 2015

![](chart.png)
Recognizing Efficacy: Endpoints

- **Histology- Premalignancy (Intraepithelial neoplasia, IEN)**
  
  **Rationale:** IEN is a recognized intermediate in causal pathway to cancer development
  
  - Identifies higher risk population
  - Potential endpoint for early phase trials

- **Identifiable populations; removal may be standard-of-care (e.g., colon adenomas, cervical neoplasia)**

- **Negative: variable rate of progression to cancer; organ/lesion dependent; may be hard to identify**
  
  - Biology of regressive vs. progressive lesions is different

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*Kelloff et al., Clin Cancer Res 2008;12:3661*
Recognizing Efficacy: Endpoints

- **Cancer-related biomarkers**
  - Processes deregulated in cancer (e.g., proliferation)
  - Regulatory/signaling pathways crucial to carcinogenesis

- **Drug effect biomarkers (PD)**

- **Imaging** – few applications in premalignancy setting

- **Caveats:**
  - Relationship between endpoint and cancer development needs to be well understood and *informative*
  - Multiple pathways to carcinogenesis
  - How much biomarker change is enough? Statistical vs. biologic relevance
# How Can We Optimize Early Phase Prevention Trials?

Table 2 | Phase II cancer prevention trial designs

<table>
<thead>
<tr>
<th>Trial type</th>
<th>Cohort</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention trial with IEN endpoint</td>
<td>High-risk individuals with IEN</td>
<td>Pre-screening for IEN is necessary</td>
</tr>
<tr>
<td>Prevention trial with a molecular endpoint</td>
<td>High-risk individuals, no IEN needed</td>
<td>Less pre-screening necessary; less informative</td>
</tr>
<tr>
<td>Advanced cancer trial with nested ‘prevention endpoint’</td>
<td>Cancer patients, with and without IEN</td>
<td>Potentially high drop-out rate owing to progressive disease; the agent must be appropriate for prevention</td>
</tr>
<tr>
<td>Adjuvant trial with nested ‘prevention endpoint’</td>
<td>Curatively treated cancer patients, with and without IEN</td>
<td>The agent must be appropriate for prevention</td>
</tr>
<tr>
<td>Presurgical model</td>
<td>Cancer patients awaiting definitive surgery</td>
<td>Limited duration of treatment, biomarker modulation only; tissue acquisition as part of ‘standard of care’</td>
</tr>
<tr>
<td>Neoadjuvant model</td>
<td>Cancer patients being treated to downstage tumour before definitive therapy</td>
<td>Mainly biomarker modulation; tissue acquisition as part of ‘standard of care’</td>
</tr>
</tbody>
</table>

IEN, intraepithelial neoplasia.

-Szabo E, Nat Rev Cancer 2006;6:867-876
Innovative Trial Designs

- Field carcinogenesis predicts heterogeneity, need to target the lesions/abnormalities most likely to progress
  - For risk assessment as well as target identification

- Sample the field using ‘omic’ technologies
  - to detect drug effects on pathways in a short time frame

-Gustafson et al. Sci Transl Med 2010;2:26ra25
How do we move forward?

- Understand the genesis and natural history of carcinogenesis
  - Understanding molecular mechanisms of carcinogenesis, TCGA of premalignancy
    - Molecularly targeted agents
    - Repurposed ‘old’ drugs
  - Persistent versus regressive premalignant lesions - who is likely to progress and why?

- Innovative early phase trial designs
  - High throughput technologies (e.g., gene expression analysis) to detect drug effects on pathways in a short time frame
  - Multiple trial designs to build a “body of evidence”
Development of Cancer: Opportunities for Intervention

- Normal
- Initiated
- Dysplasia (Mild, Moderate, Severe)
- Carcinoma In Situ
- Invasive Cancer

Prevention
Early Detection
Treatment